HITRIplus
Heavy Ion Therapy Research Integration

Prostate (part 2)

Trial Design

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Treatment options

- Treatment for Pca is usually based on the clinical stage
- Unfavorable intermediate- and high-risk cancer are currently treated with a comprehensive approach
- Radiotherapy (RT) has become a major therapeutic option (NCCN guidelines)
- External Beam RT (IMRT, IGRT, SBRT, V-MAT) or Brachytherapy (LDR, HDR)
- High dose RT improves biochemical control (boost on DIL) and bRFS
- RT with a dose of 70-80 Gy, combined with ADT improves survival in intermediate/high risk groups
- Genitourinary toxicity increases from 70 Gy versus 80 Gy or more
- Hypofractionated RT is not inferior to conventional RT
- It is crucial to balance tumor control and toxicity response (long-term)

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Clinical Results

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Clinical outcomes of high-dose RT

IMRT	Dose/fractions	% 5-year bRFS (LR/IR/HR)	% Late toxicity (GI/GU)
Kupelian (2007)	70 Gy/28	94/83/72	6/7
Cahlon (2008)	86.4 Gy/48	98/85/70	7/16
Guckenberger (2014)	73.9-74.8 Gy/32-33	88/80/78	4.8/22.4
Leing (2017)	60-66 Gy/20-22	100/56-89/56	7.3/12.2
Shimizu (2017)	72.6-74.8 Gy/ 33-34	95/92/77	10.9/7.2
SBRT	**Dose/fractions**	**% 5-year bRFS (LR/IR/HR)**	**% Late toxicity (GI/GU)**
King (2013)	35-40 Gy/5	95/84/81	NA/NA
Fuller (2018)	38 Gy/4	100/81-90/NA	3.4/14.7
Vuolukka (2020)	36.25 Gy/5	100/87.5/80	NA/NA

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Ishikawa H et Al. Int J Urol 2022 (modified)

Clinical outcomes of Particle Therapy

PBT	Dose/fractions	% 5-year bRFS (LR/IR/HR)	Late toxicity (GI/GU)
Bryant (2016)	**72-82 Gy/36-41**	**99/94/74**	**0.6/2.9 (G3)**
Iwata (2018)	**70-80/63-66 Gy/35-40/21-22**	**97/91/83**	**4.1/4**
Takagi (2021)	**73.9-74.8 Gy/32-33**	**99-100/90-93/76-88**	**4/2.2**
CIRT	**Dose/fractions**	**% 5-year bRFS (LR/IR/HR)**	**G3 late toxicity (GI/GU)**
Ishikawa (2012)	**35-40 Gy/5**	**90/97/88**	**1.9/6.3**
Nomiya (2016)	**38 Gy/4**	**92/89/92**	**0.4/4.6**

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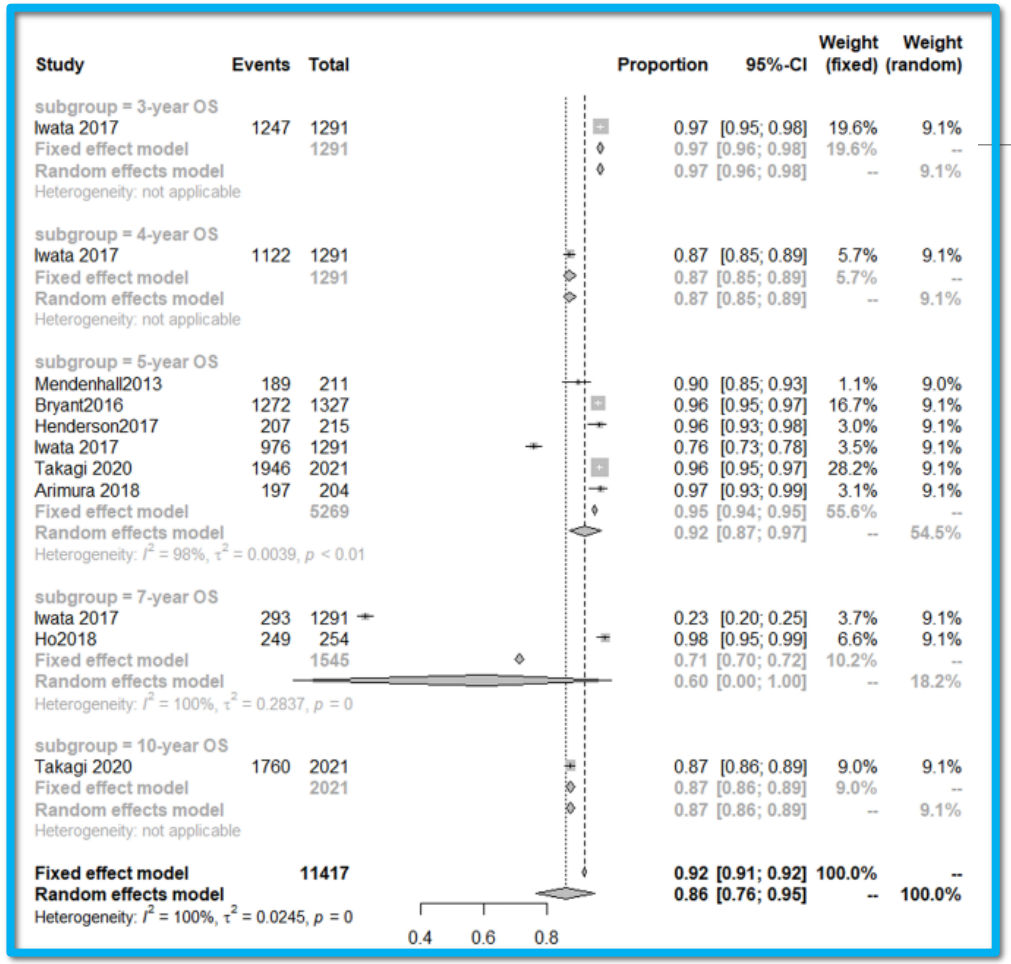
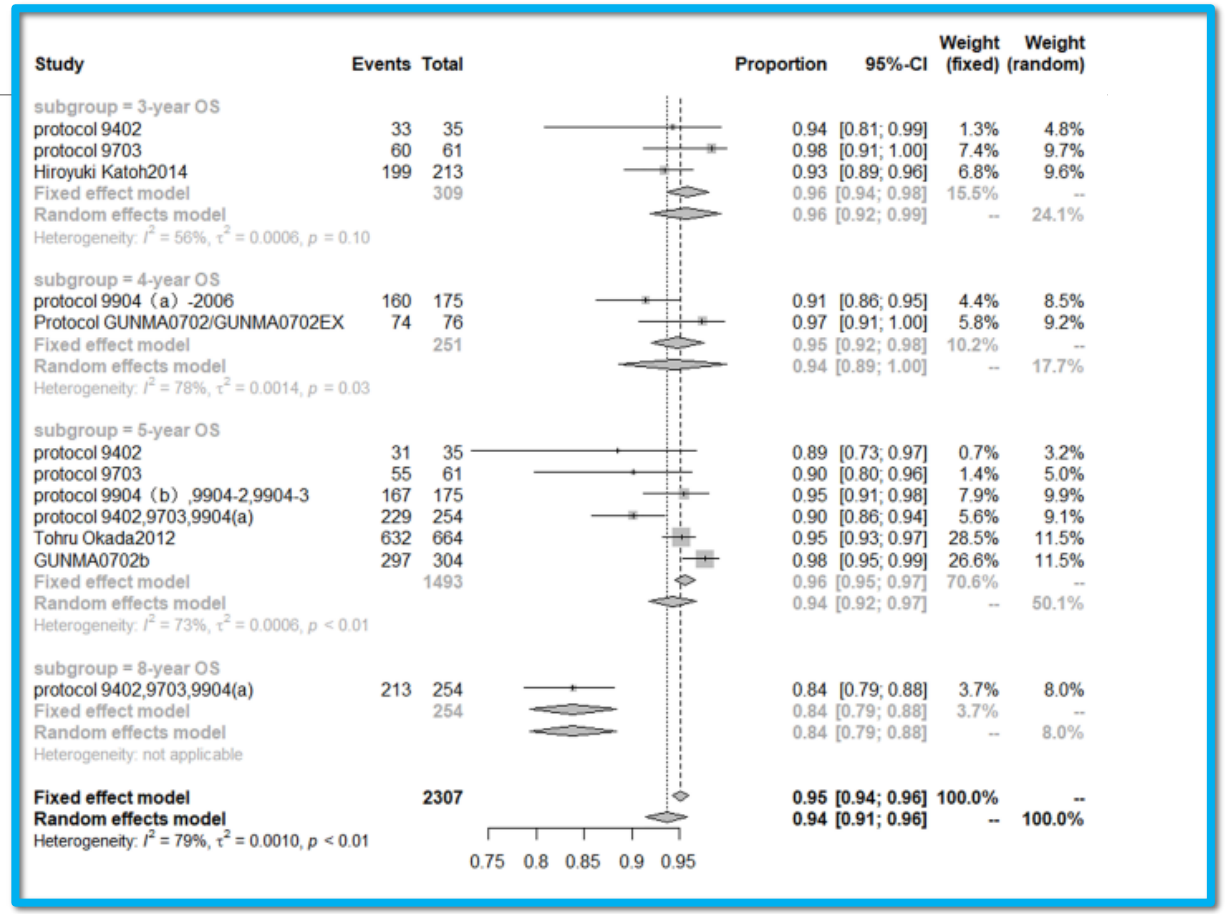
Ishikawa H et Al. Int J Urol 2022 (modified)

Clinical Efficacy of Proton Therapy and CIRT. Meta-analysis





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Meta-analysis. Summary of findings

5-years OS for CIRT: 94% (89% bRFS)
5-years OS for PBT: 92%

G2+ GI toxicity CIRT: 2.2%
G2+ GI toxicity PBT: 4%
G2+ GU toxicity CIRT: 5%
G2+ GU toxicity PBT: 5%

Ultrafractionated vs hypofractionated and conventional RT

(Lehrer EJ et al, Radiother Oncol 2020)

5-years DFS: 85.1% (CFRT), 86% (HFRT), 85% (UHRT)

G2+ GI toxicity: 12.1% (CFRT), 14.6% (HFRT), 10% (UHRT)

G2+ GU toxicity: 19.4% (CFRT), 20.4% (HFRT), 18% (UHRT)

Outcomes	Carbon ion radiotherapy		Proton Beam Therapy	
	№ of participants (studies)	Certainty of the evidence (GRADE)	№ of participants (studies)	Certainty of the evidence (GRADE)
OS follow up: range 36 months to 120 months	2307 (8 observational studies)	⊕◯◯◯ VERY LOW	11417 (7 observational studies)	⊕◯◯◯ VERY LOW
LCR follow up: range 36 to 60 months	1004 (6 observational studies)	⊕⊕◯◯ LOW	-	-
BRF follow up: range 36 months to 96 months	2211 (8 observational studies)	⊕◯◯◯ VERY LOW	-	-
acute gastrointestinal toxicity (AGI) follow up: range 6 months to 96 months	7753 (8 observational studies)	⊕◯◯◯ VERY LOW	4057 (8 observational studies)	⊕◯◯◯ VERY LOW
(LGI) follow up: range 6 months to 96 months	11304 (12 observational studies)	⊕◯◯◯ VERY LOW	10856 (12 observational studies)	⊕◯◯◯ VERY LOW
AGU follow up: range 6 months to 96 months	10038 (9 observational studies)	⊕◯◯◯ VERY LOW	6164 (12 observational studies)	⊕◯◯◯ VERY LOW
LGU follow up: range 6 months to 96 months	12384 (12 observational studies)	⊕◯◯◯ VERY LOW	11575 (15 observational studies)	⊕◯◯◯ VERY LOW

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Ongoing Trials

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12 Fractions Carbon Ion Radiotherapy for Localized Prostate Cancer

ClinicalTrials.gov ID NCT04724577

To explore the optimal dose of 12 fractions of CIRT for prostate cancer in Shanghai

The dose of 51.6 GyE in 12 fractions is currently widely used in Japan, and clinical studies of 51.6GyE/12Fx have also been carried out for SBRT. There are some differences in equipment and carbon ion TPS used between Japan and our center. This phase I study explores the optimal dose of 12 fractions of CIRT

Intervention/Treatment
Radiation: carbon ion radiotherapy • dose escalation radiotherapy with five levels of dose from 54GyE/12Fx to 58.8GyE/12Fx

Endpoints: acute toxicity, bRFS, OS, PFS

Carbon Ion Radiotherapy for the Treatment of Localized Prostate Cancer

ClinicalTrials.gov ID NCT02739659

To assess the feasibility and safety of CIRT for the treatment of in Chinese localized prostate cancer

To determine the MTD of CIRT and evaluate the efficacy at MTD. Partecipants will be treated with escalating dose regimes to evaluate the MTD in terms of acute and subacute toxicity observed during and within 6 months after CIRT. Once the MTD is determined, the MTD will be used as the recommended dose to patients fulfilling the inclusion criteria in the phase II part of the trial

Endpoints: treatment-related adverse events as assessed by the NCI-CTCAE v4.0, bRFS, OS, PFS

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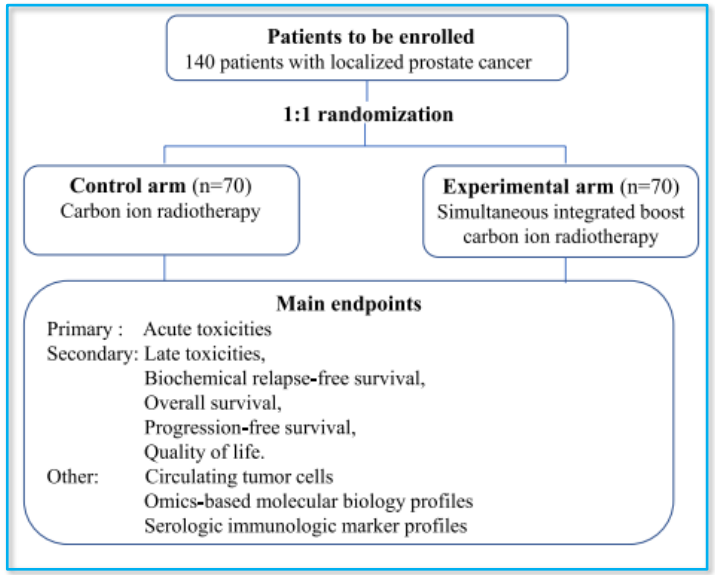
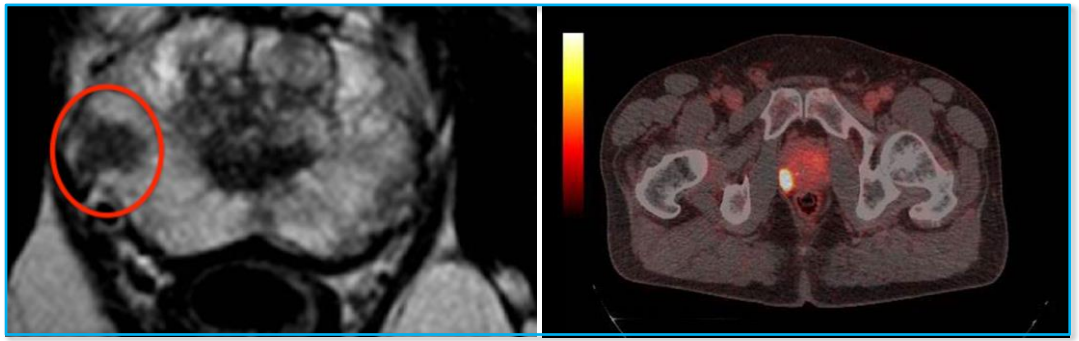
Functional imaging-guided carbon ion irradiation with simultaneous integrated boost for localized prostate cancer: study protocol for a phase II randomized controlled clinical trial



Determination of the target boost area of prostate cancer is the key to the implementation of SIB technology

Based on EAU, NCCN, and ESUR guidelines, mpMRI is used for target area (sensitivity = 0.87; specificity = 0.68), together with 68Ga-PSMA PET/CT (sensitivity = 80%; specificity = 97%)

Arm A, dose 65.6GyE in 16 fractions (4.1GyE/fr) in 4 weeks
Arm B, dose 65.6GyE in 16 fractions (4.1GyE/fr) and boost 72GyE in 16 fractions (4.5GyE/fr)



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Phase II multi-institutional clinical trial on a new mixed beam RT scheme of IMRT on pelvis combined with a carbon ion boost for high-risk prostate cancer patients

Prospective, multicentric (CNAO, IEO, INT), phase II open-label trial with 65 patients enrolled

Anticipated CIRT boost to the whole prostate-proximal third of the seminal vesicles [16.6 Gy (RBE)/4 fractions, equivalent to 28 Gy/14 fr (α/β = 3 Gy) or 24 Gy (α/β = 1.5 Gy) followed by IMRT (45-50.4 Gy in 1.8-2 Gy/fraction) to the pelvic lymph nodes, prostate, and seminal vesicles, with long term ADT

Primary endpoint safety and feasibility in terms of acute toxicity

NCT 02672449 (clinicaltrials.gov)

Mixed-beam approach for high-risk prostate cancer: Carbon-ion boost followed by photon intensity-modulated radiotherapy. Dosimetric and geometric evaluations (AIRC IG-14300)

CIRT superior to full cycle IMRT in redicing dose to rectum, bladder, anal cavity and penile bulb, with optimal TV coverage. IMRT better for dose to femoral heads

High level of accuracy is required for deformable organs

Dosimetric Impact of Inter-Fraction Anatomical Changes in Carbon Ion Boost Treatment for High-Risk Prostate Cancer (AIRC IG 14300)

Dose distribution reproducible for target coverage and OaRs sparing

Mixed-Beam Approach for High-Risk Prostate Cancer Carbon-Ion Boost Followed by Photon Intensity-Modulated Radiotherapy: Preliminary Results of Phase II Trial AIRC-IG-14300

No GI/GU toxicities G2+. QoL scores satisfactory

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Marvaso G, Orecchia R et Al. Tumori J 2017; Gugliandolo SG, Orecchia R et Al. Phys Med 2020
Russo S, Orecchia R et Al. Front Oncol 2021; Marvaso G, Orecchia R et Al. Front Oncol 2021

CIRT is superior to Photons?

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Patient selection methods

- **Clinical decision-making tools**

  - Informed decision-making
  - Diagnosis/clinical indications list
  - Multi-disciplinary team consensus
  - Cost-effectiveness

- **Dose comparative methods**

  - Comparative planning/dosimetry
  - NTCP (between plans)
  - Knowledge-based DVH prediction
  - Influence diagram
  - Different prediction softwares
  - Radiobiologic Markov model
  - Risk analysis/long-term outcomes

- **Hybrid techniques**

  - PRODECIS (computer generated model that selects modality based on dosimetry, toxicity levels and cost-effectiveness)

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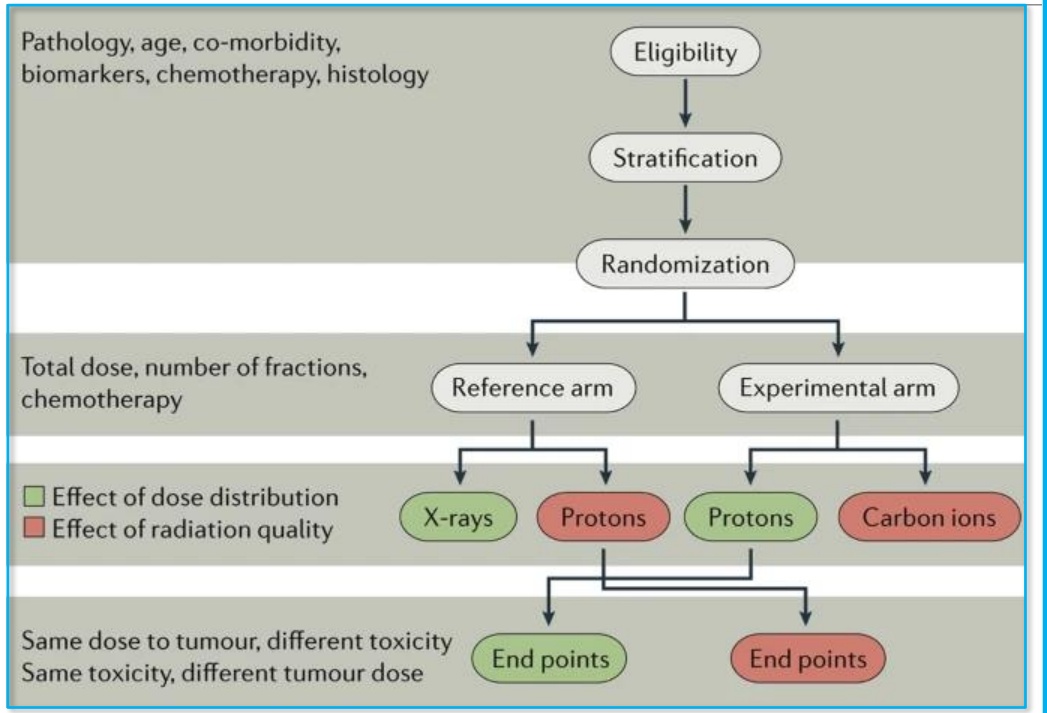
Clinical trial design



Physical advantages from dose deposition should be associated with biological advantages, to be exploited in clinical trials

Radiobiology of response to charged particles different from photons, that cannot be bridged with a simply multiplicative factor (RBE): different radiation qualities have different therapeutic properties

In trials delivering same dose to tumor, TCP will be the same with both modalities and only significant differences in NTCP, if detected, will show any superiority
To detect significant variations in NTCP, trials should incorporate patients with tumors associated with high rates of radiation-induced adverse events. These rates are now decreasing at state-of-the-art facilities

In most trials, toxicity remains the primary end point, and OS end point in highly prevalent tumors should be encouraged

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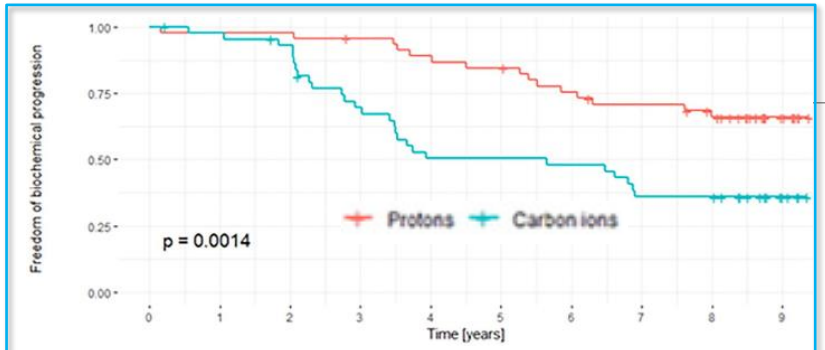
Durante M, Orecchia R, Loeffler JS. Nature Rev 2017

Changes in RBE-models

Results of a prospective randomized trial on long-term effectiveness of protons and carbon ions in prostate cancer: LEM I and α/β=2 Gy overestimates the RBE



5-year bRFS in proton meets literature-based expectations of similar outcomes for similar RBE-weighted doses

For CIRT bRFS was significantly lower, in spite of the same nominal RBE-weighted total and fractional doses of 66 Gy(RBE) and 3.3 Gy(RBE), respectively, corresponding to an EQD2 of 87.46 Gy (α/β = 2 Gy)

Dose prescription based on Japanese data suggested a CIRT total dose of 66 Gy(RBE) in 20 fractions

RBE-weighted doses for CIRT in Japan used different RBE-models and cannot directly be transferred to European facilities

HIT clinical CIRT data indicates that RBE and RBE-weighted dose have been underestimated

The nominal dose of 20 × 3.3 Gy(RBE) is clinically equivalent to a normo-fractionated photon dose of <70–72 Gy

Clinical relevance in a real patient cohort of taking the underlying biological dose calculation method

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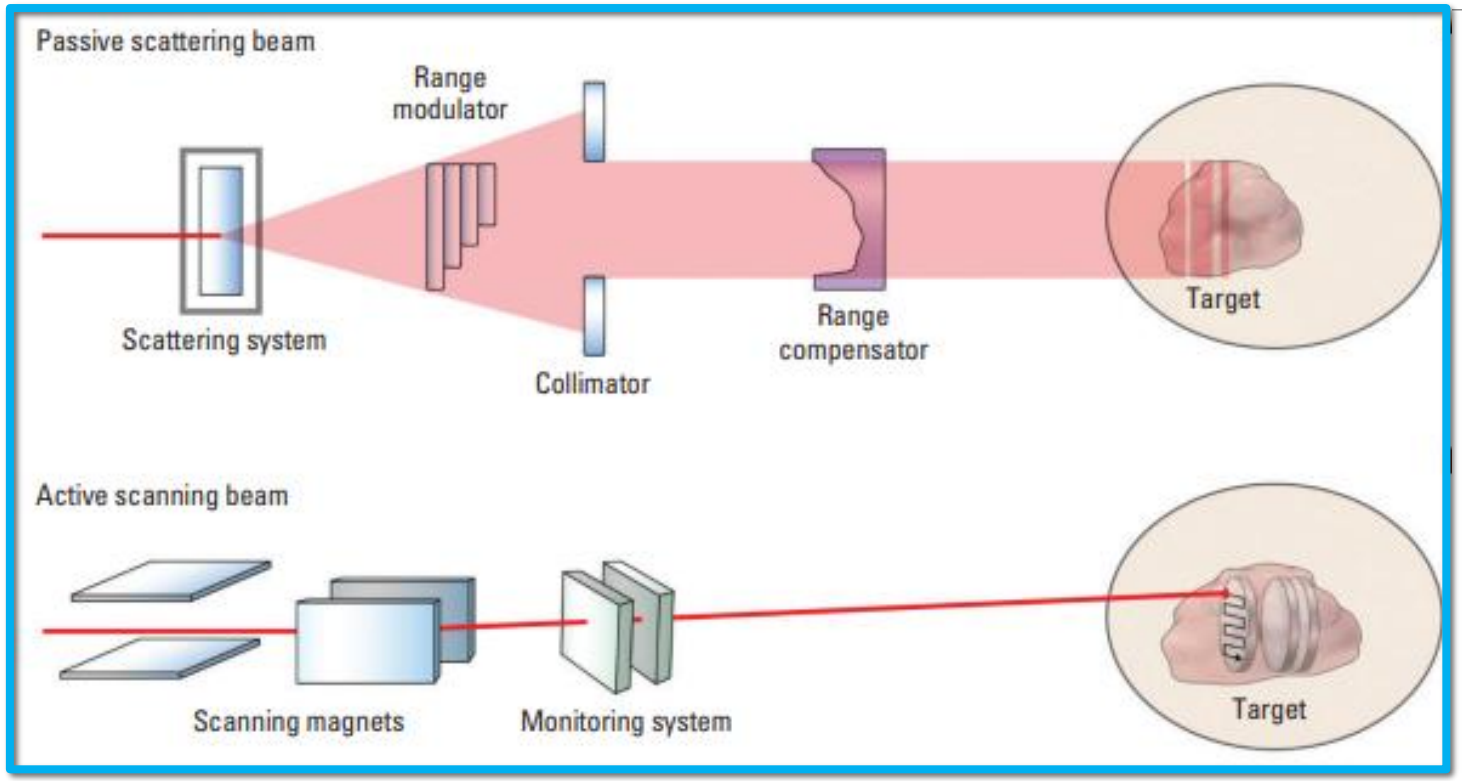
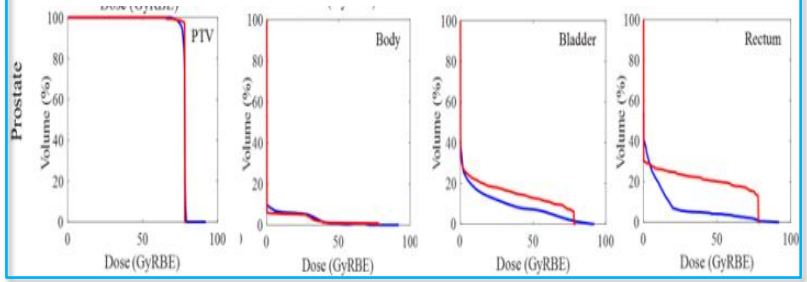
Changes in beam delivery



Prostate	Bladder	V80	0	0	0
		V75	7.161	2.6	-4.56
		V70	9.33	3.6	-159.1
		V65	9.71	4.5	-115.7
	Rectum	V75	14.92	6.28	-137.5
		V70	16.75	8.50	-97
		V65	17.63	8.73	-101.9
		V60	18.28	9.01	-102.9
	PTV	D95 (Gy)	76.7	75.44	-1.26
		D5(Gy)	81.07	78.1	-3.8
		Mean dose (Gy)	79	77.8	-1.2



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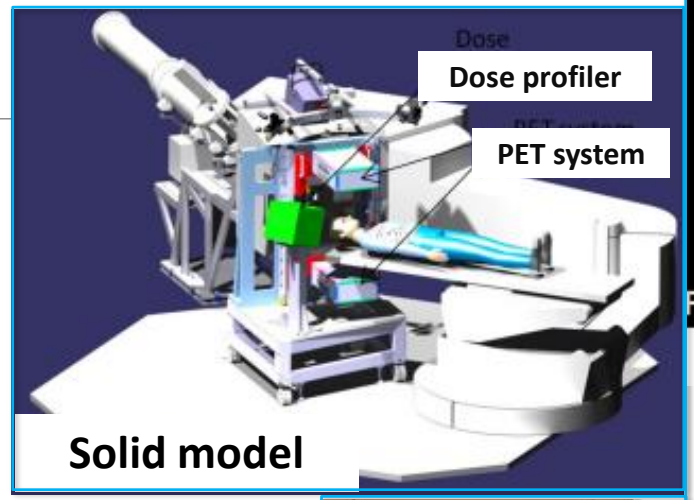
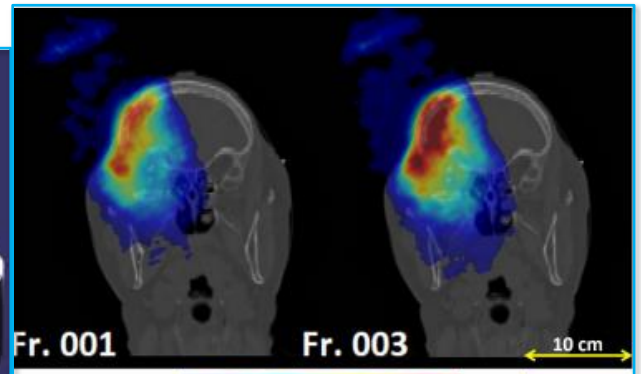
In-vivo monitoring by in-beam PET

Nuclear interactions of particles with tissue result in production of β^+ isotopes, which decay emitting a positron, that annihilates into a 511 keV photon pair

Detection of these photon pairs by means of a PET system yields an activity image, indirectly correlated with dose

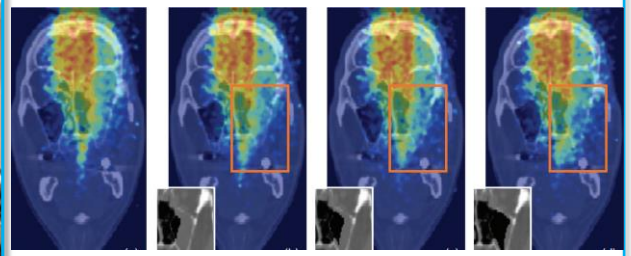


Solid model



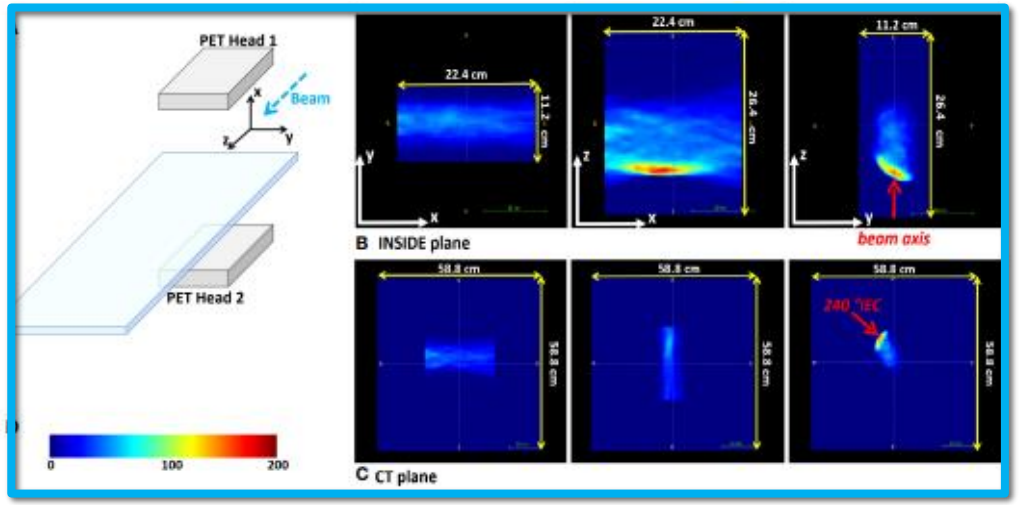
Reconstructed real-time images

INSIDE I-B PET



Evolution of PET signal with gradual emptyng of the sinonasal cavity

INSIDE (*INnovative Solution for In-beam Dosimetry in hadronthErapy*) since 2019 is under clinical trial (ClinicalTrials.gov NCT03662373)



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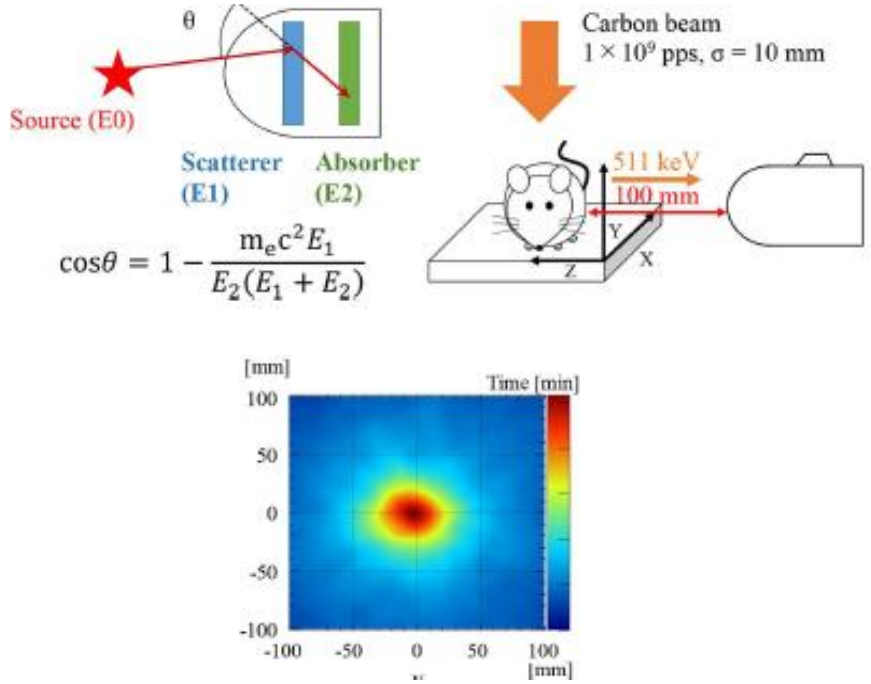
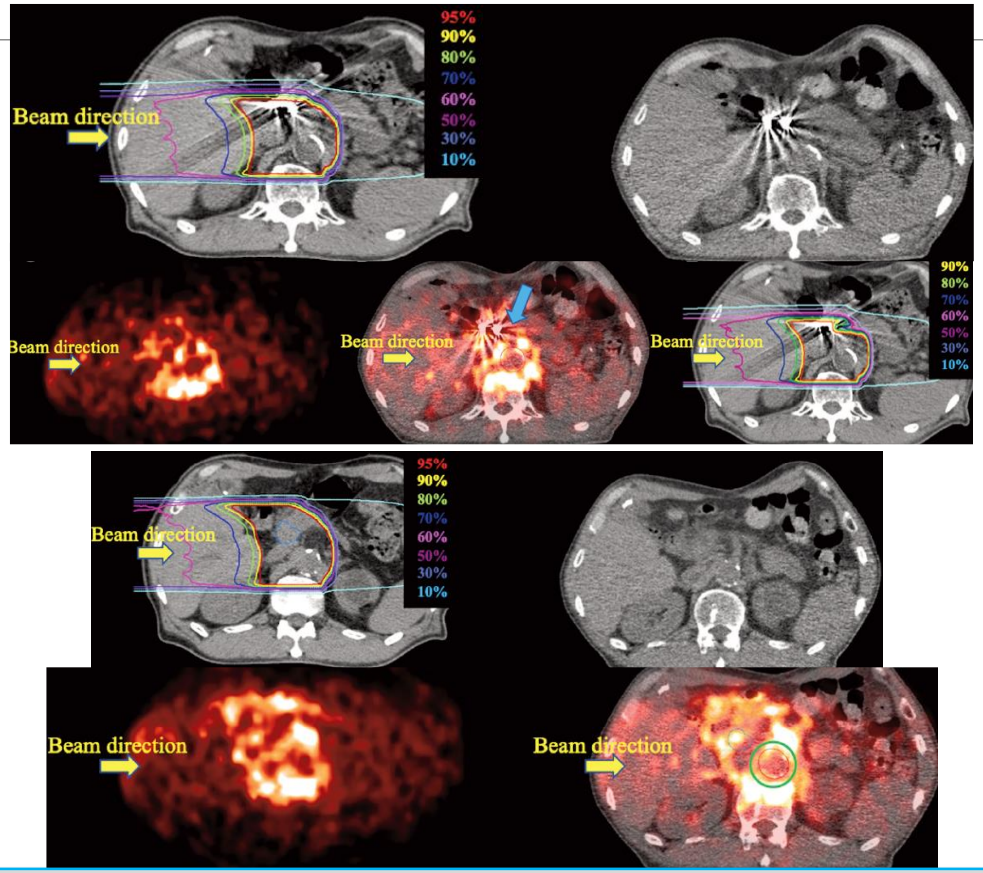
Bisogni MG et Al. J Med Imag 2017; Fiorina E et Al. Phys Med 2018; Moglioni M et Al. Front Oncol 2022

Auto-Activation PET (AAPET)

Use of a Si/CdTe Compton Camera for *In vivo* Real-Time Monitoring of Annihilation Gamma Rays Generated by Carbon Ion Beam Irradiation



Visualisation of Range Shortening in Carbon Ion Beams and Washout of Positron Emitter: First-in-Human Report



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Shiba S et Al. Front Oncol 2020; Shiba S et Al. In vivo 2021

What we need to translate in Clinical Trials

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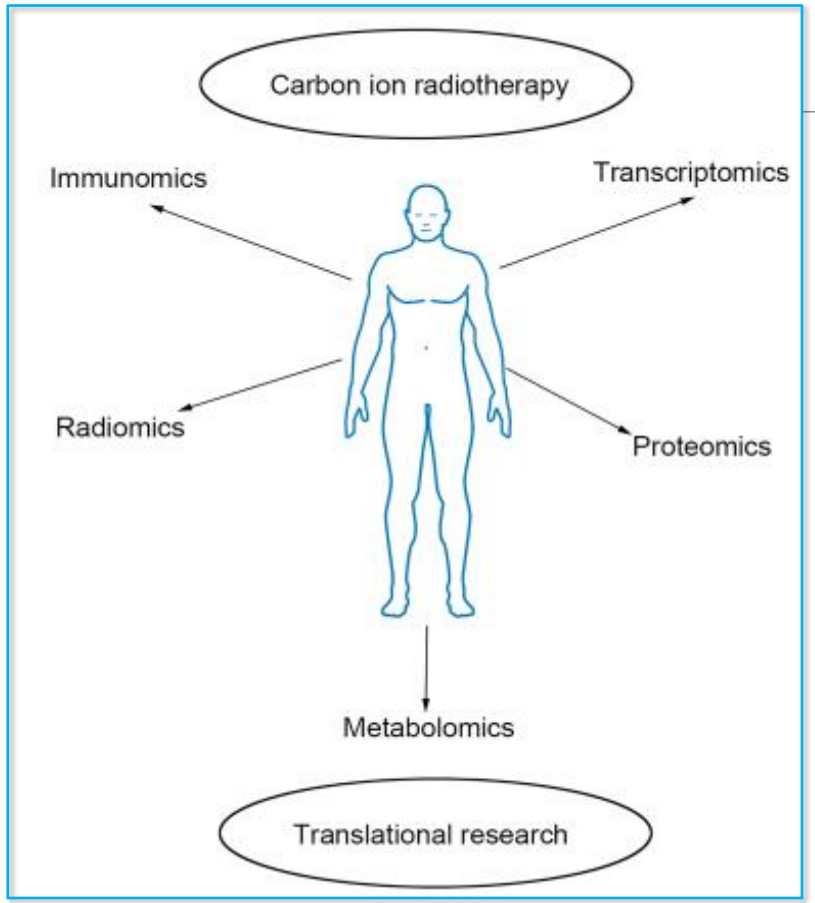
Biologically driven trials



Selection of patients and trial design based on radiobiology

Patient stratification according to the expression levels of molecular biomarkers (radio-resistance, hypoxia, other intratumoural heterogeneities, especially to the different cell lineages present in cancer-stem-cell niches, changes in microenvironments, …) which could be specifically targeted

Testing treatment combinations in trials necessary to determine the most beneficial treatments

Preclinical data and possibility of sparing immune cells suggest importance of comparative trials of combinations with immunotherapy and other targeted drugs

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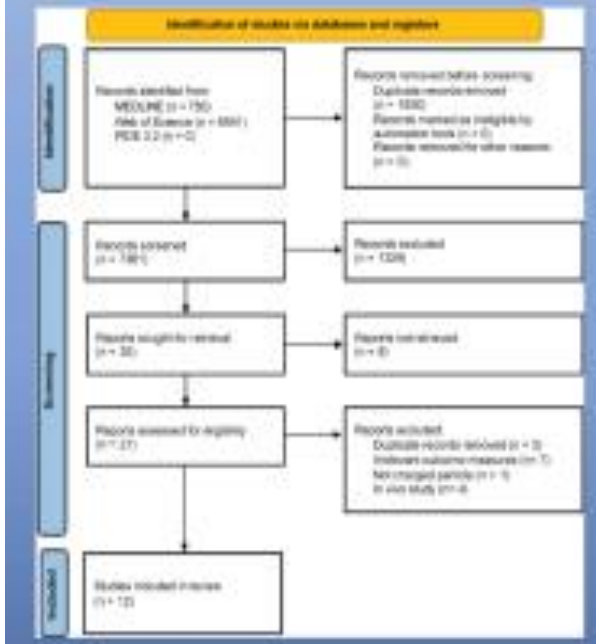
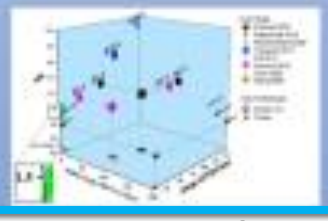
Durante M, Orecchia R, Loeffler JS. Nature Rev 2017; Chen X et Al. Front Oncol 2021

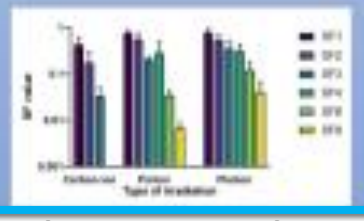
Radiobiological advantages

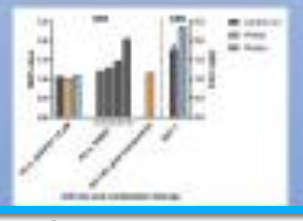
Does Particle Radiation Have Superior Radiobiological Advantages for Prostate Cancer Cells? A Systematic Review of in Vitro Studies



Including 12 studies







RBE: 0.94-1.52 (proton), 1.67-3.7 (carbon)
SF of 2 Gy: 0.55 (proton), 0.17 (carbon), 0.53 (photon)
OER: 1.77 (carbon), 2.32 (photon)
PNKP inhibitor and gold nanoparticles favorable sensitizing agents
More G0-/G1- or G2-/M-phase arrest, more expression of γ-H2AX, more apoptosis, lower motility/migration ability

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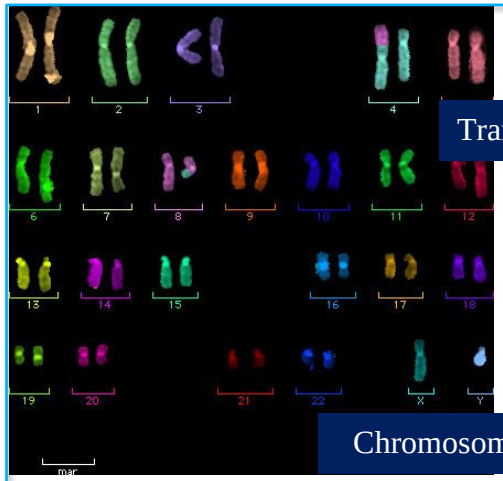
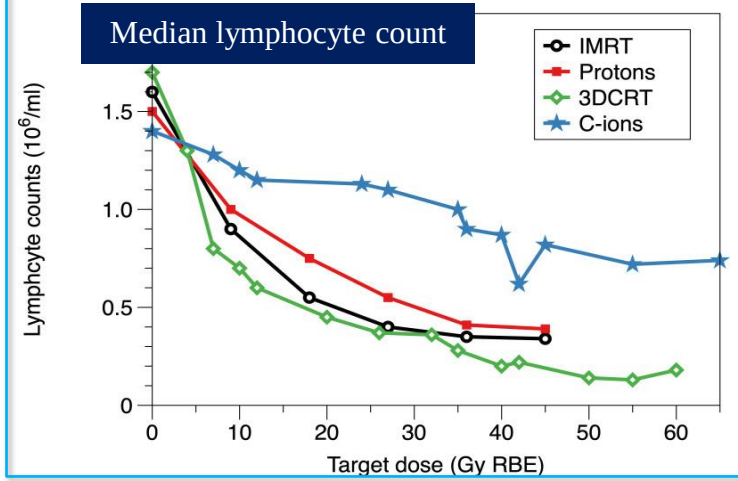
Changes in peripheral blood lymphocytes



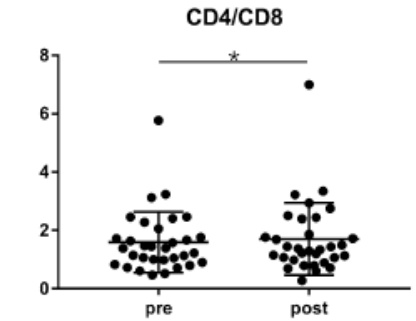
Translocation in 4 and 8

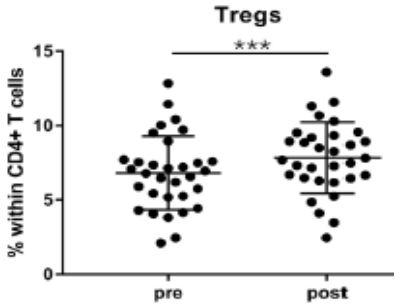
Chromosomal aberration assay

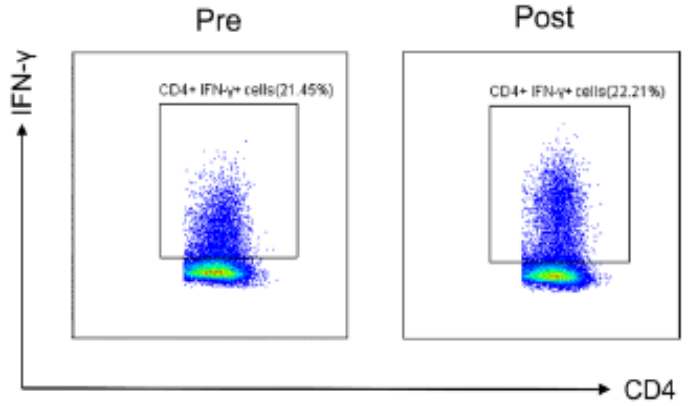
Median lymphocyte count



Immunomodulatory effects of carbon ion radiotherapy in patients with localized prostate cancer







Negligible damage to peripheral lymphocytes
Increased CD4/CD8 ratio, a marker of anti-tumor cellular immunity
Increased production of TNF
Increased circulating Tregs (regulatory T cells), a predictive marker for response
Higher doses induced more powerful tumor cytotoxicity and antigen release

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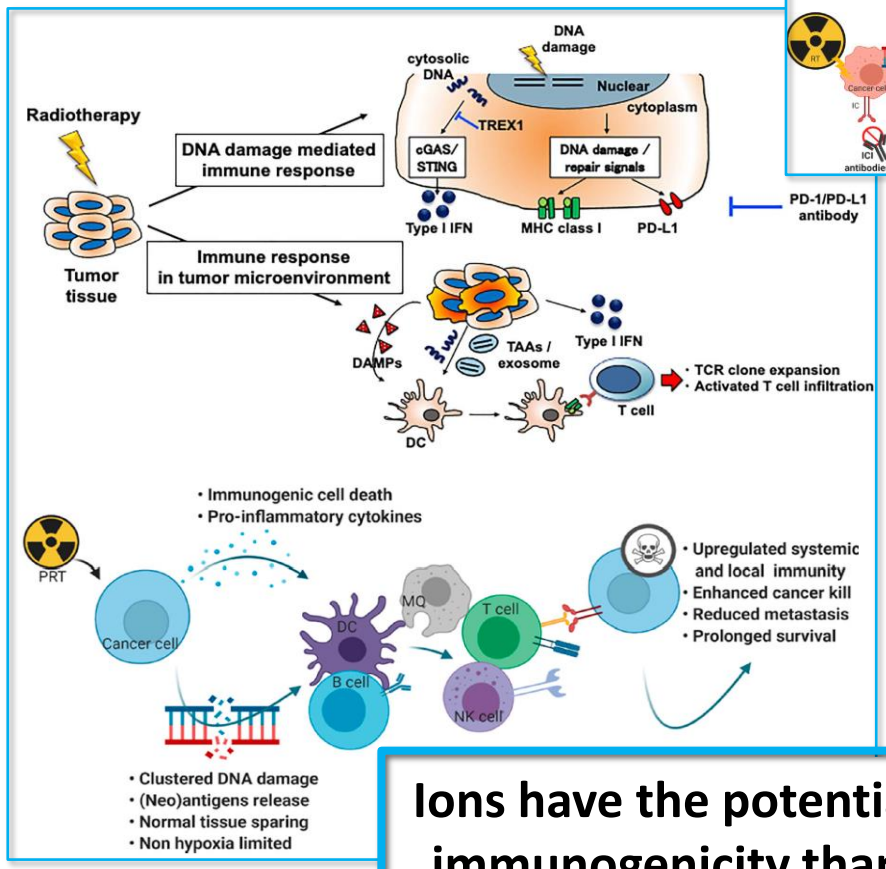
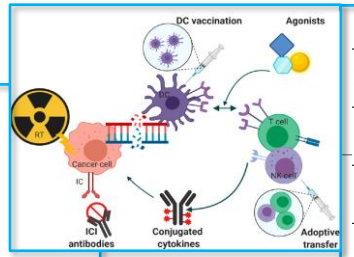
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Durante M, Formenti S. Br J Radiol 2020; Hu W et Al. J Cancer Res Clin Oncol 2022

Ions-Immunotherapy combination





	Identifier	Pathology	RT Dose	IO	Dose	Status	Study Type
PrRT	NCT02648997	Meningiomas	Unknown	Nivolumab * Ipilimumab *	N: 1 mg/kg for 3 weeks I: 3 mg/kg for 3 weeks	Recruiting	Open-label Phase-II
	NCT03267836	Meningiomas	fRT; 5 × 0.04 Gy Total 0.2 Gy	Avelumab *	Concurrent RT, 10 mg/kg, every 2 weeks for 3 months	Recruiting	Phase I
	NCT03539198	Head and neck cancer	fRT; 5× Total 35–45 Gy	Nivolumab *	Before and after RT, Q2/week for 2 weeks	Recruiting	Observational
	NCT03764787	Unknown	Unknown	a-PD-1	Unknown, for 1 year	Not yet recruiting	Phase I/II
	NCT03765190	Neoplasm metastasis	Unknown	a-PD-1	Unknown	Not yet recruiting	Phase I/II
	NCT03818776	Non-small cell lung cancer	fRT; 20–23× Total 60–69 Gy (cardiac sparing)	Durvalumab	1500 mg Q4W, max. 12 months (to 13 doses/cycles)	Recruiting	Early Phase I
	NCT03087760	Non-small cell lung cancer	Reirradiation, unknown	Pembroluzimab	Unknown	Recruiting	Phase II
	NCT02444741	Non-small cell lung cancer	fRT, 15× low dose, Total unkown	Pembroluzimab	Unknown dose for 21 days, up to 16 cycles	Recruiting	Phase I/II
CIRT	NCT04143984	Locally recurrent nasopharyngeal carcinoma	fRT; 21 × 3 Gy Total 63 Gy	Camrelizumab *	C: 200 mg i.v. every 2 weeks for a year maximum	Not yet recruiting	Phase II/III
CIRT	NCT03705403 **, [102]	Non-small cell lung cancer	SABR	Darleukin	C: 15 Mio IU, 6 cycles, 3 infusions within one cycle, every 3 weeks	Not yet recruiting	Phase II

Ions have the potential to inflict higher immunogenicity than photons due to more unrepaired DNA damage and genomic mutations or instability

Synergy with Dendritic Cell vaccination, Adoptive Transfer of NK and T cells, Agonist administration, Conjugated Antibodies, or Immune Checkpoint Inhibitors

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Immune checkpoint inhibitors and Carbon iON radiotherapy In solid Cancers with stable disease (ICONIC)

A multicenter, open-label, nonrandomized phase II trial to assess feasibility and activity of the addition of CIRT to immune checkpoint inhibitors in cancer patients with SD after pembrolizumab given as standard-of-care

Primary end point is objective response rate, secondary end points are safety, survival and disease control rate

Translational research is an exploratory aim

Planned sample size: 27 patients

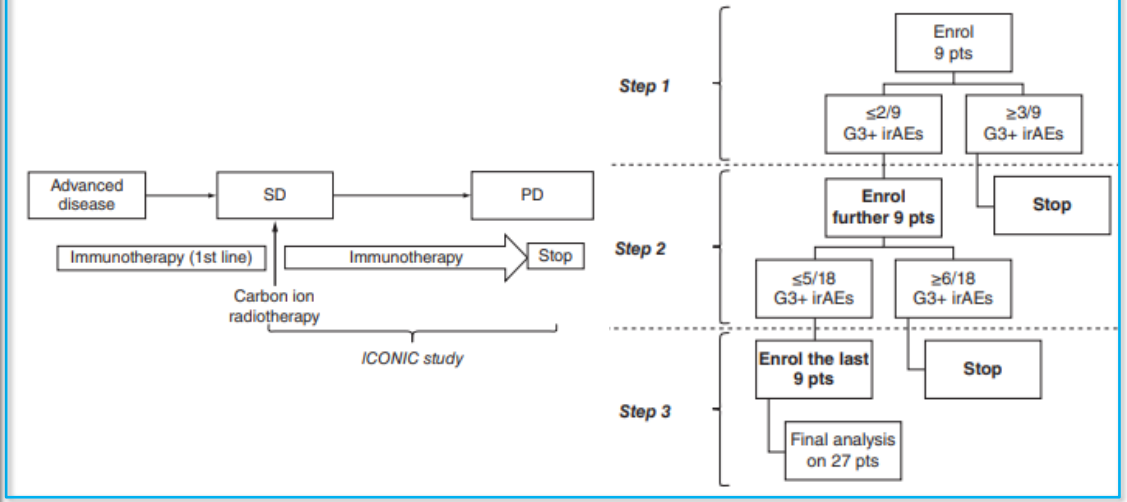
The study combination will be considered worth investigating if at least four objective responses are observed

If the null hypothesis is rejected, ICONIC will be the first proof of concept of feasibility and clinical activity of addition of CIRT to immune checkpoint inhibitors in oncology

This study will provide controlled data about the safety of this unprecedented therapeutic combination

NCT05229614 (ClinicalTrials.gov)

Cancer	Setting	Grade ≥3 AEs (%)
Melanoma	First and second line	17
NSCLC	First line	26.6
	First line	18
HNSCC	First line	55
Urothelial	First line	15.7



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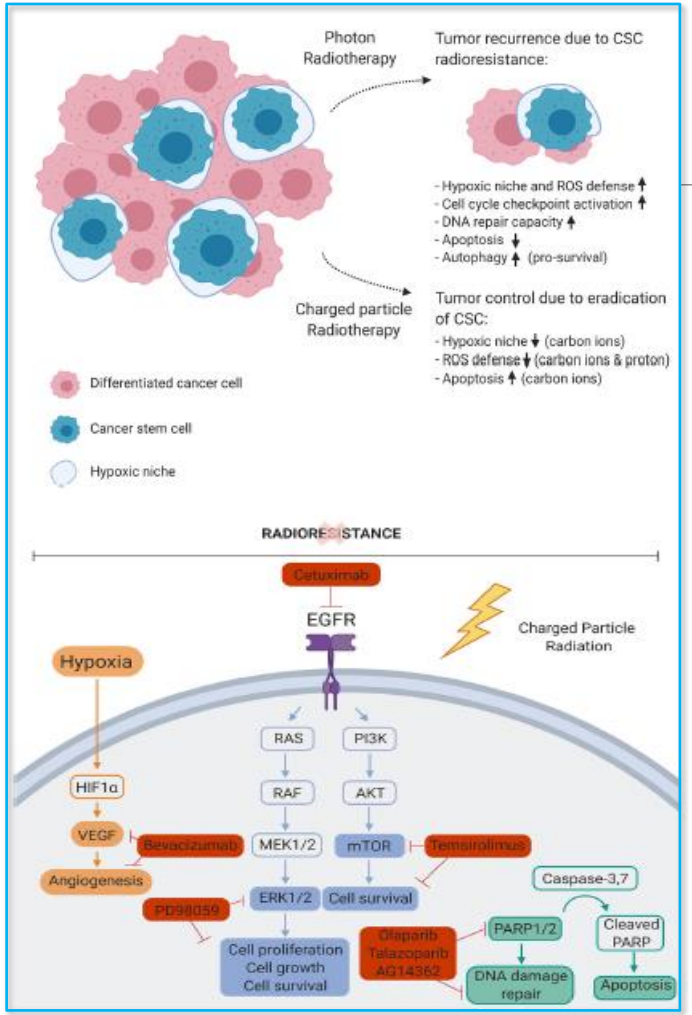
C-ions combined with targeted therapy



Target	Small Molecule Inhibitor	Doses (Gy)	Cells	Outcome
EGFR	Cetuximab	1–4	Human laryngeal squamous cell carcinoma	Inhibition of invasion
mTOR	Temsirolimus	0.1–3	Hepatocellular carcinoma	Additive effects in cell killing
	Rapamycin	1–5	Chondrosarcoma cells	Sensitization of the C-ion effects
PARP1/2	Olaparib	1–5	Human pancreatic cancer cells	Sensitization of the C-ion effects
	PARP-1 knockdown	1–4	HeLa cells	Sensitization of the C-ion effects
	Talazoparib	2	Human glioblastoma stem-like cells	Sensitization of the C-ion effects
DNA-PKcs	Genistein	2–6	Human glioblastoma cell lines	Sensitization by inhibition of NHEJ
	NU7026	2	Human lung normal and cancer cells	Sensitization by inhibition of NHEJ
	NU7026	1–4	Hela cells, human breast cancer cells	Sensitization mediated by telomere-end capping
Hsp90	TAS-116	1–5	Hela, lung cancer and normal human fibroblasts, tumor xenografts	Radio-sensitization of both X-rays and C-ions
	PU-H71	1–7	HeLa derivative, human lung normal and cancer cell lines	Sensitization of cancer cell but not of normal cells
Hedgehog	GANT61	0.2–4	Prostate cancer cells Pediatric medulloblastoma	Sensitization and reduced migration
	GANT61	0.2–4	Human breast cancer cells	Reduced cell migration

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Konings K et Al. Front Oncol 2020; Tinganelli W & Durante M. Cancers 2020

Genomic Classifiers in Personalized Prostate Cancer Radiation Therapy Approaches: A Systematic Review and Future Perspectives Based on International Consensus

Genomic classifiers (GCs) are promising tools to improve risk-stratification in primary and oligo-/metastatic patients in addition to existing classifications

GCs might guide treatment decisions in terms of RT-field definition and intensification/ deintensification in various disease stages

Additional studies of GCs as prognostic biomarkers form the basis for future studies addressing predictive capabilities of GCs to optimize RT and systemic therapy

Trial number	Study type	Patient characteristics	Applied GC	Treatment decision based on GC
NCT04513717 (NRG-GU009)	Parallel phase 3, randomized	NCCN high risk	Decipher	Escalation or de-escalation of systemic therapy
NCT05100472 (SHORTER)	Phase 2, nonrandomized	NCCN high risk	Decipher	ADT de-escalation
NCT05050084 (NRG-GU10)	Parallel phase 3, randomized	NCCN unfavorable intermediate risk	Decipher	Escalation or de-escalation of systemic therapy
NCT04025372 (INTREPID)	Phase 2, randomized	NCCN intermediate risk	Decipher	N/A (GC is required and serves as stratification variable)
NCT05169970	Phase 2, nonrandomized	NCCN unfavorable intermediate risk	Decipher	Inclusion of elective pelvic lymphatics in RT field
NCT02783950 (G-Minor)	Randomized, parallel assignment	RPE with pT3 or positive margins	Decipher	Adjuvant treatment decision (RT or ADT)
NCT04984343 (FORT)	Phase 2, randomized	NCCN low and intermediate risk	Decipher	N/A (GC >0.6 serves as inclusion criterion)
NCT04396808	Crossover assignment, randomized	NCCN low and intermediate risk	Decipher, Prolaris, and Oncotype DX	N/A (effect of GC on treatment decision)
NCT02723734 (VANDAAM)	Cohort	NCCN low and intermediate risk	Decipher	N/A (effect of GC on outcome prediction)
NCT03495427 (subgroup of VANDAAM)	Cohort	NCCN low and intermediate risk	Decipher	N/A (concordance between GC and PSMA-PET)
NCT03371719 (NRG-GU006)	Phase 2, randomized	SRT	PAM50 gene expression	N/A (gene expression clustering)
NCT03770351	Cohort	NCCN low and intermediate risk	Decipher ProstateNext	N/A (effect of GC on outcome prediction)
NCT03141671	Phase 2, randomized	SRT	Decipher	N/A (high-risk Decipher score as inclusion criterion)
NCT04134260	Phase 3, randomized	SRT	Decipher PAM50 gene expression	N/A (effect of GC on outcome prediction)

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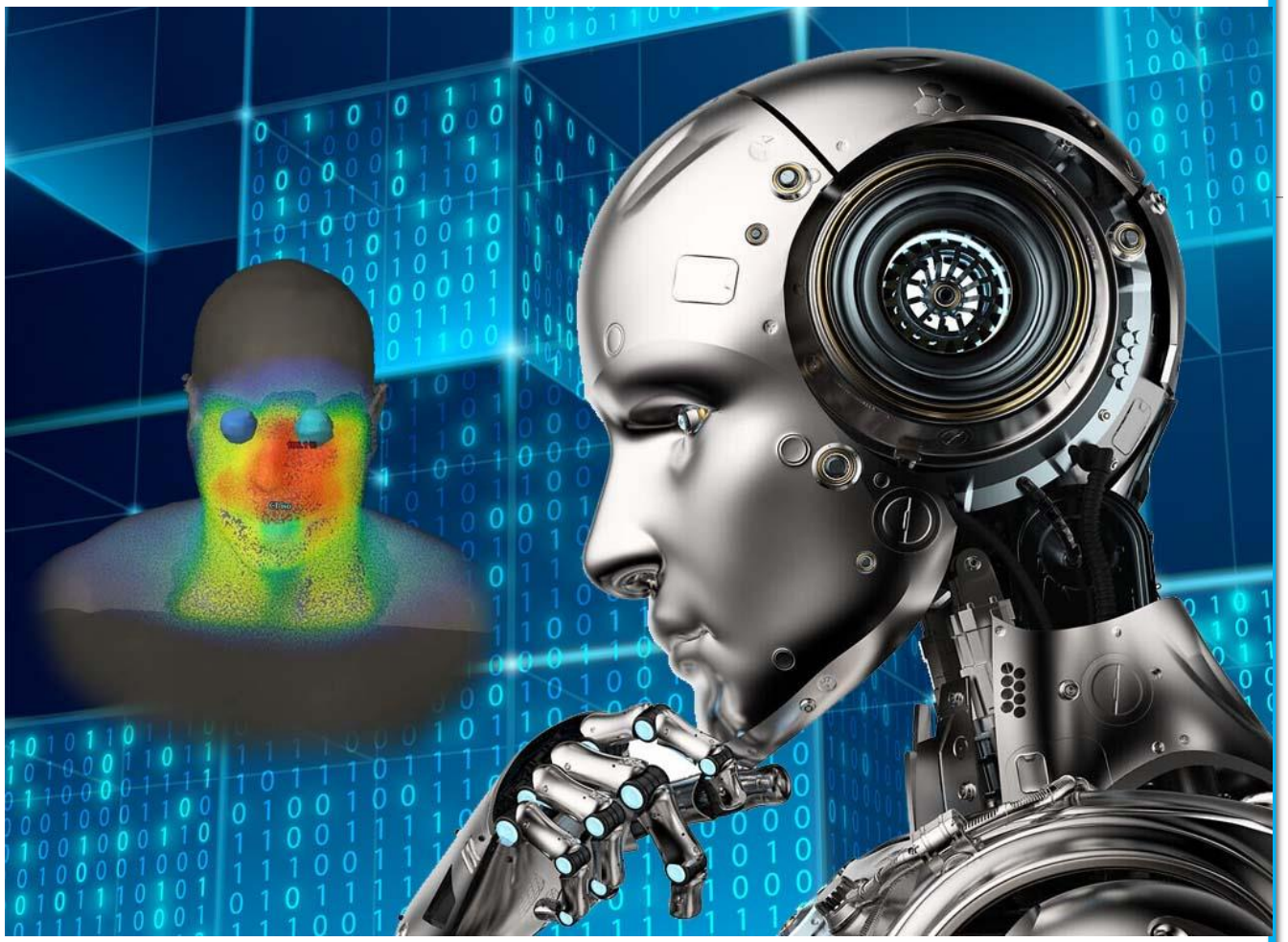

Radiomics, Dosiomics, Radiogenomics and AI

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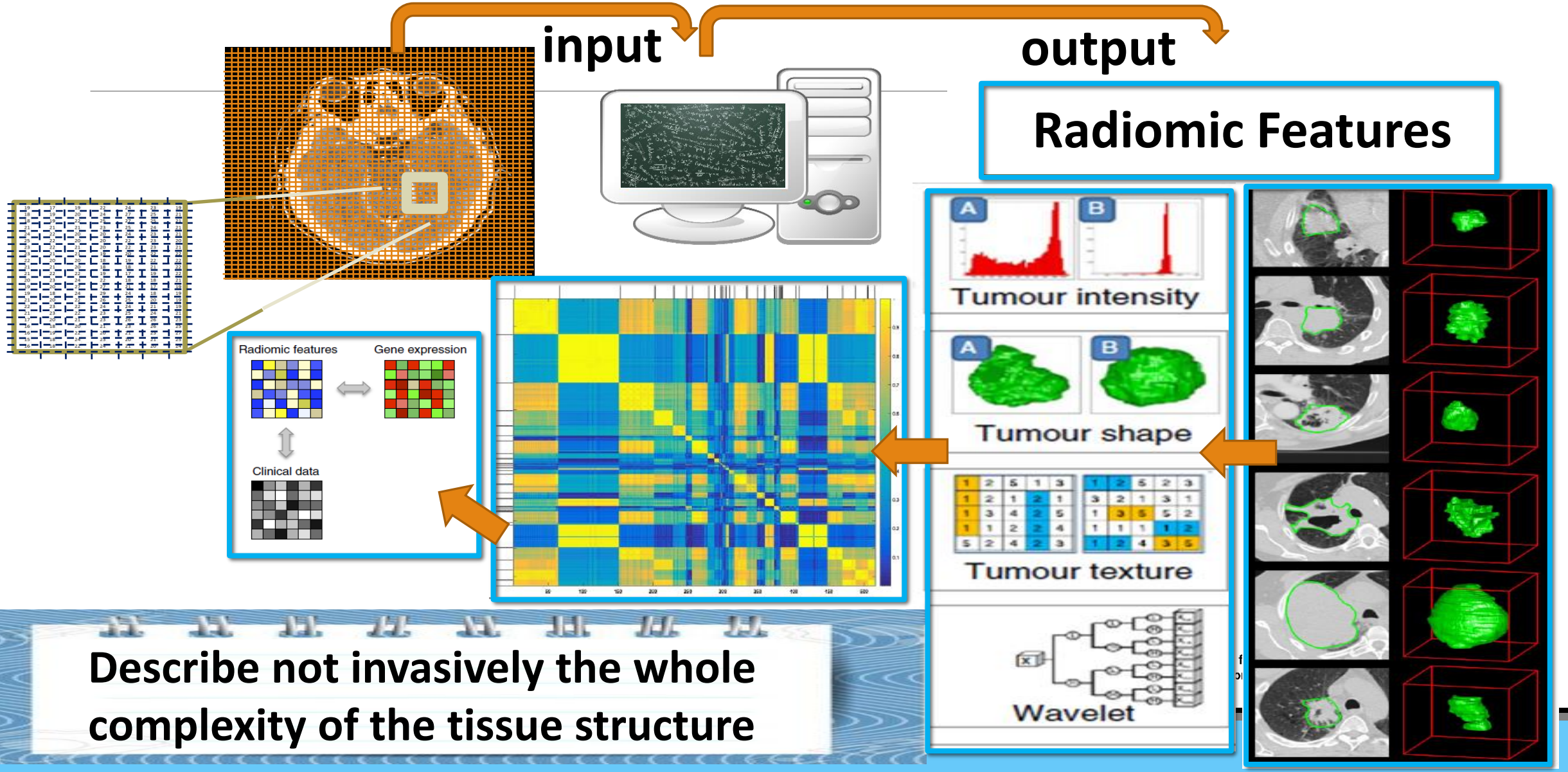
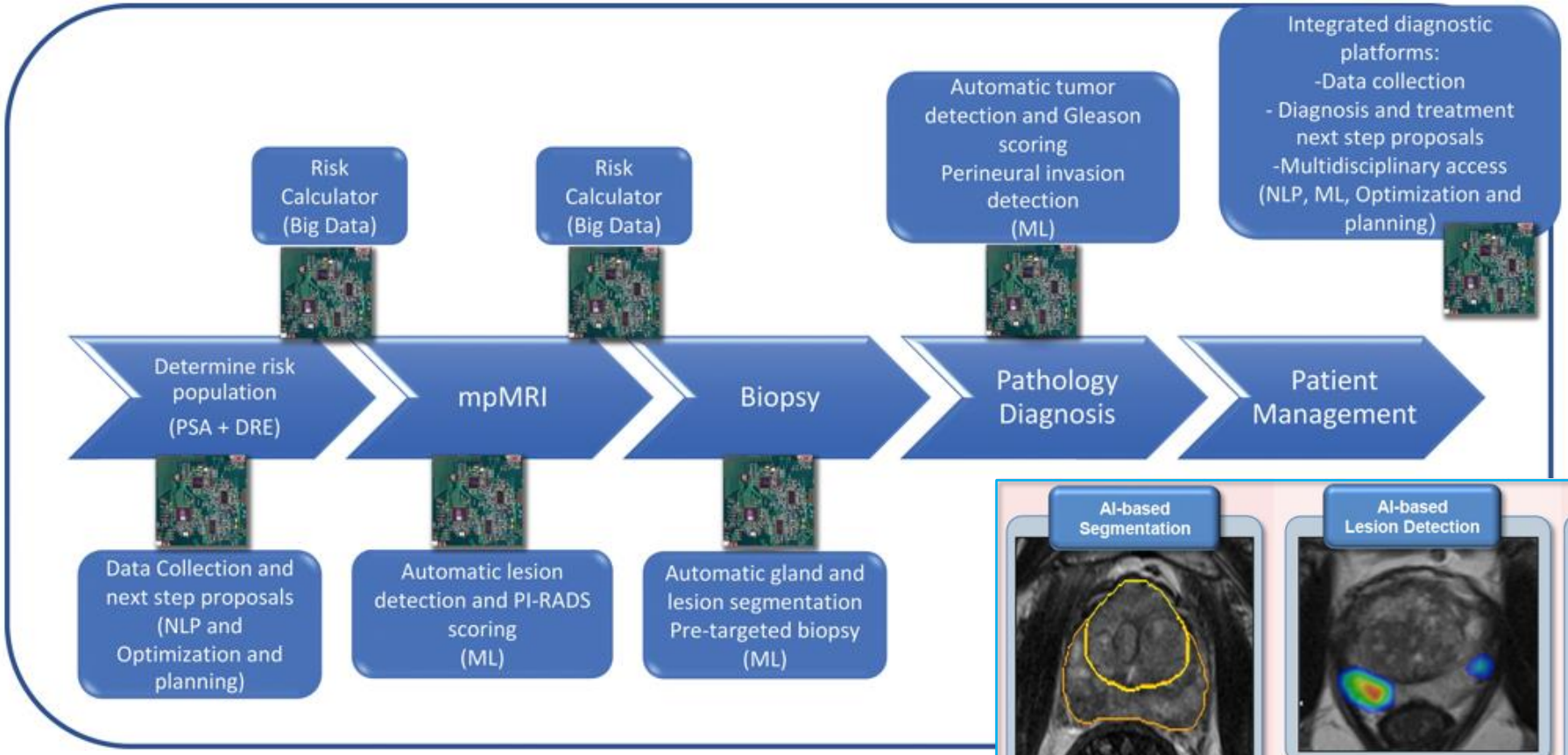
Images are more than picture: they are DATA !



Describe not invasively the whole complexity of the tissue structure

AI assisted diagnosis/staging



Prostate gland segmentation, detection and classification of lesions with an automatic PI-RADS score by using AI for T2-w, DWI, and DCE sequences

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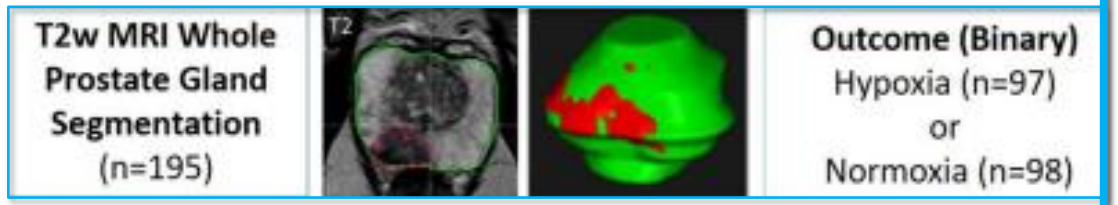
Mata LA et Al. RadioGraphics 2021

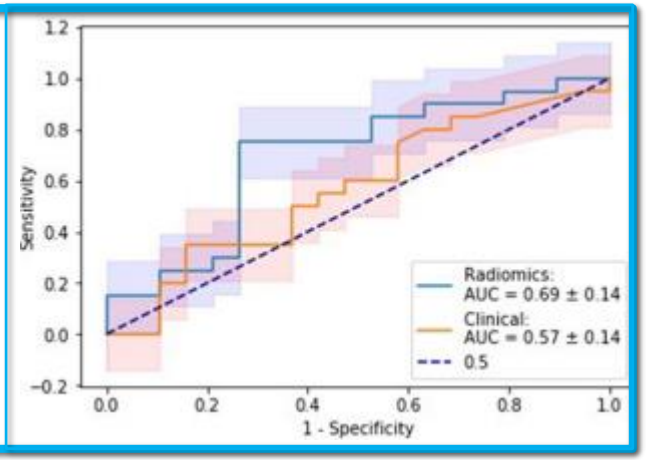
Prediction of prostate tumour hypoxia using pre-treatment MRI-derived radiomics: preliminary findings

To develop a machine learning (ML) model based on radiomic features (RF) extracted from whole prostate gland MRI for prediction of tumour hypoxia

195 patients with high-grade pCa and RT pre-treatment MRI
Cancers were dichotomised as normoxic or hypoxic using a biopsy-based 32-gene hypoxia signature (Ragnum signature)
Prostate segmentation performed on axial T2-weighted (T2w) sequences using RayStation (v9.1)



PyRadiomics (v3.0.1) used to extract RFs
6 different ML classifiers for distinguishing hypoxia trained and tuned using 5 different feature selection models and 5-fold cross-validation with 20 repeats
Best performance on hypoxia prediction using ridge regression (AUC of 0.69)
5 selected RFs included textural and wavelet-transformed features
Whole prostate MRI-radiomics has the potential to non-invasively predict tumor hypoxia which may be helpful for individualized treatment optimization



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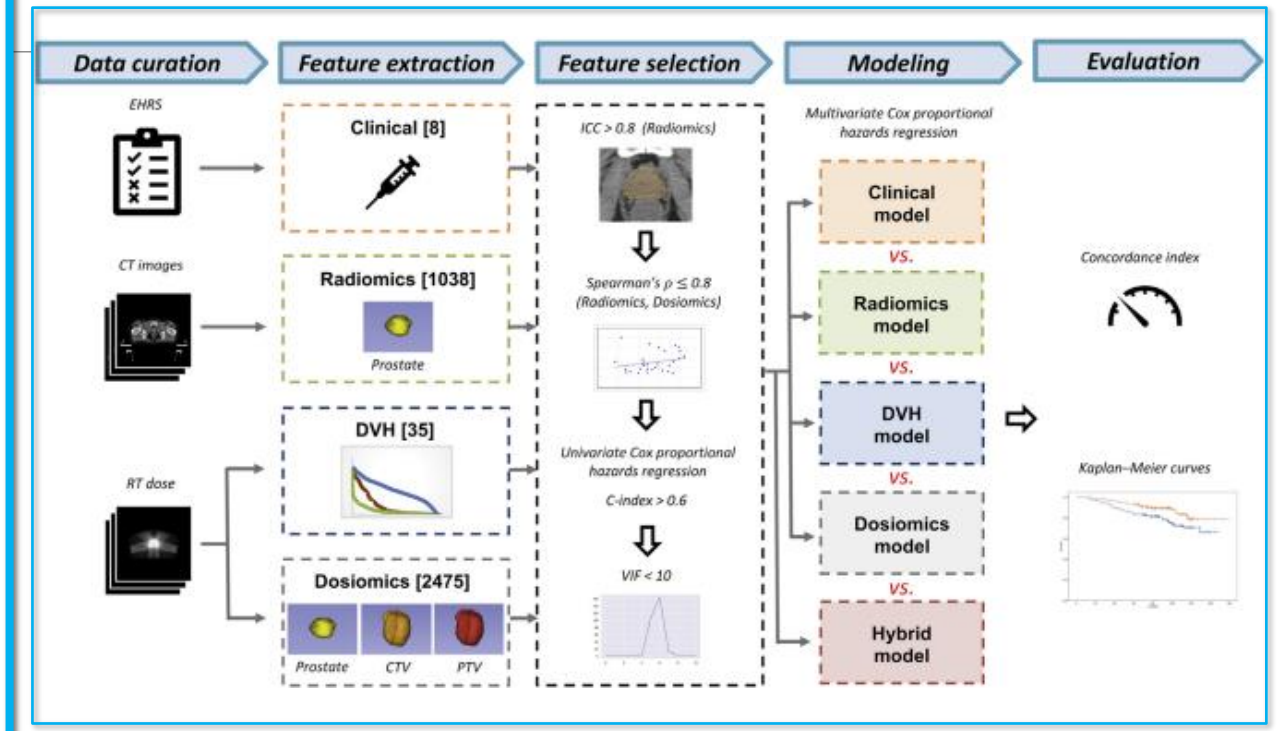
Dosiomics, a new tool for personalized treatment

- Extraction of features from the patient's 3D RT dose distribution to obtain specific spatial and statistical information
- Parameterization of dose distribution in particular ROIs by intensity, textural and shape-based features allows a high complexity level of description, distinct from those obtained from DVHs
- Integration of dosiomics with DVHs can constitute an advanced tool to evaluate RT plan quality, identifying a new metrics
- Introduction of dosiomics features into TCP and NTCP models can overcome current limitation of these models



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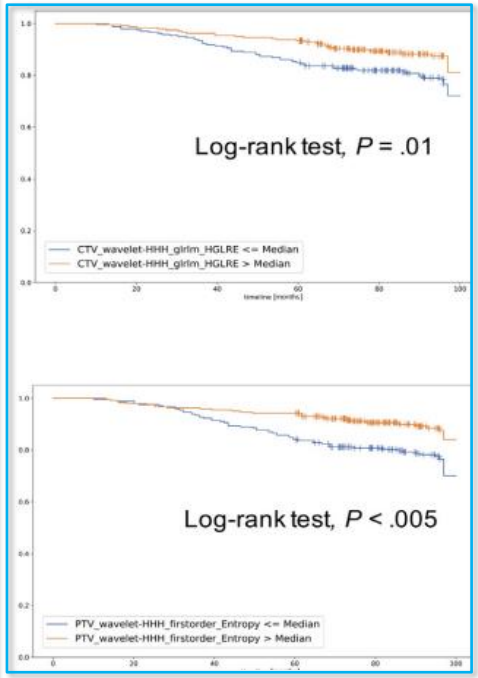
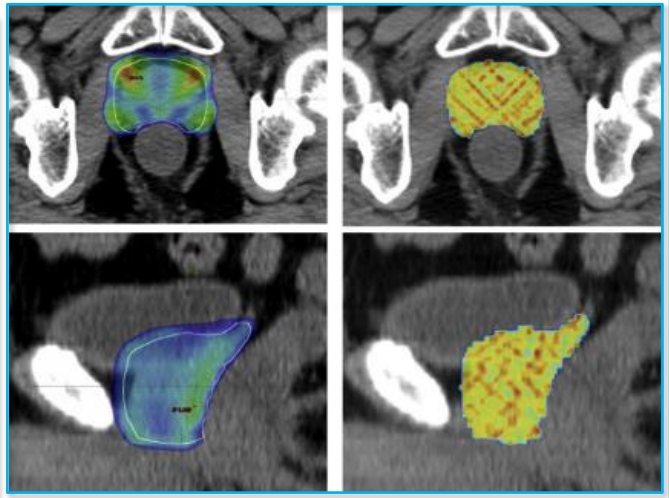
Dosiomics analyses

Dose-Based Radiomic Analysis (Dosiomics) for Intensity Modulated Radiation Therapy in Patients With Prostate Cancer: Correlation Between Planned Dose Distribution and Biochemical Failure



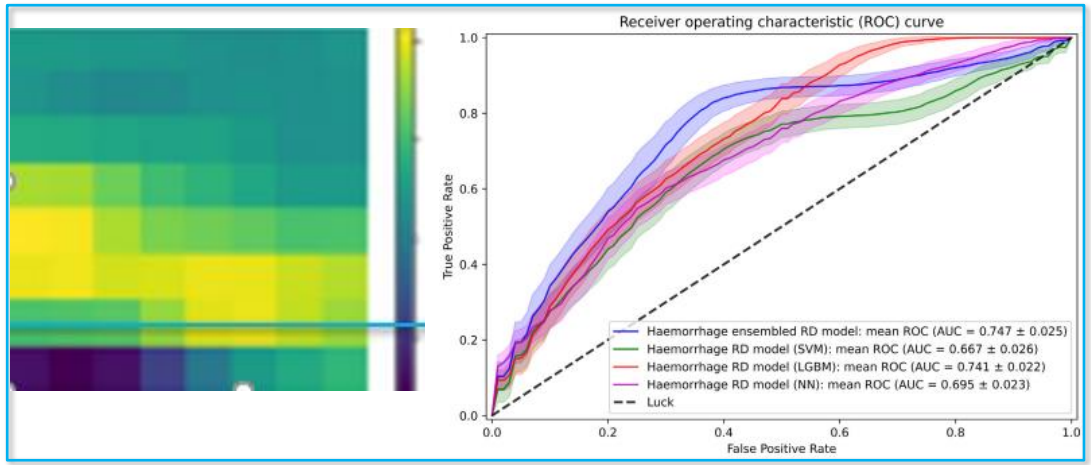


Dosiomic features extracted from CTV significantly correlate with bF in low and high grade PCa

Machine-learning with region-level radiomic and dosimetric features for predicting radiotherapy-induced rectal toxicities in prostate cancer patients

To build ML models to predict radiation-induced rectal toxicities for 3 clinical endpoints (proctitis, haemorrhage, GI)

Region-level pre-treatment CT radiomic features, combined region-level dosimetric features, improve the model prediction performance



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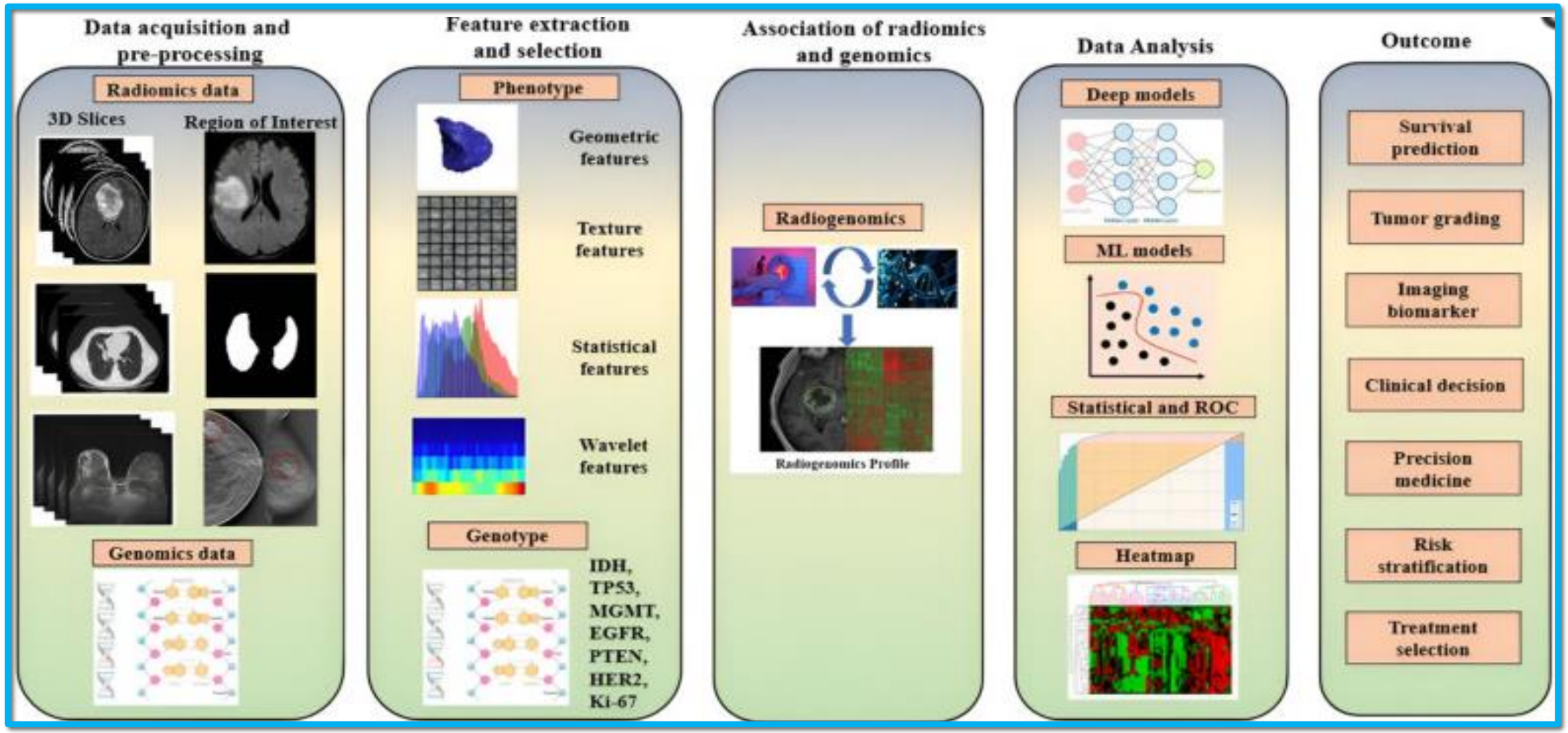
Murakami Y et Al. Int J Radiation Oncol Biol Phys 2022; Yang Z et Al. Radiother Oncol 2023

Radiogenomics pipeline



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Radiogenomics and toxicity

Analysis of individual genetic variation that affect the response of normal tissue to radiation (prediction of radiotoxicity)

The Problem

Adverse reactions in normal tissue after radiation limit the dose to tumor cells

The Challenge

Identify individual traits that allow prediction of increased risk of developing radiotoxicity (80% of variation in clinical response due to patient-related factors)

Analysis of germline variants in patient's DNA

Individual response

Analysis of radiation-induced gene expression patterns in patient's normal fibroblast/lymphocytes

The Goal

Identify germline variants and somatic epigenetic (transcription) factors modulating biological responses of normal tissues to radiation

The Plan

Establish a gene-based predictive test for normal tissue radiosensitivity

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Overview of radiogenomics literature for Pca management

Reference	Molecule Studied	Imaging Performed	Results
McCann et al. [	PTEN	MRI	Perfusion imaging contrast uptake, T2-weighted signal-intensity skewness
Stoyanova et al.	General gene expression	MRI	Radiomic signatures
Renard-Penna et al.	RNA expression signature derived from cell cycle proliferation genes (Prolaris®)	mpMRI	Correlation with Gleason score ($r = 0.199$, $p = 0.04$) and PIRADS sum score ($r = 0.26$, $p = 0.007$)
Jamshidi et al.	Whole-exosome DNA sequencing	mpMRI	No statistically significant linear correlation between individual mutations and mpMRI imaging parameters or PIRADS scores ($p = 0.3$)
Houlahan et al.	Small nucleolar RNAs	mpMRI	Elevated snoRNA abundance may be a novel hallmark of nimbotic tumors (AUC: 0.87; 95%CI: 0.75–0.99)
Li P et al.	Differentially expressed genes	MRI	MRI visibility (AUC: 0.86), progression-free survival HR = 2.53 (1.55–4.11), $p < 0.001$ BCR-free survival HR = 1.3 (1.04–1.63), $p = 0.021$
Eineluoto et al.	PTEN and ERG	MRI	MRI-invisible lesions had less PTEN loss and ERG-positive expression compared with patients with MRI-visible lesions (17.2% vs. 43.3%, $p = 0.006$; 8.6% vs. 20.0%, $p = 0.125$)
Hectors et al.	40 gene expression signatures plus Decipher®	MRI	Prediction of Gleason score of 8 or greater (AUC 0.72) and prediction of a Decipher® score of 0.6 or greater (AUC 0.84).
Li L et al.	Decipher®	MRI	Model outperformed the prediction using PIRADS v2 (AUC = 0.67), and comparable performance with Gleason grade group (AUC = 0.80)
Sun et al.	Full transcriptome genetic profiles	mpMRI	Weak association of mpMRI features and hypoxia gene expression ($p < 0.05$).
Fischer et al.	Gene and miRNA expression (Alanyl membrane aminopeptidase, microRNA-mir-217, mir-592, mir-6715b)	mpMRI	T2c and T3b prostate cancer stages being highly correlated with aggressiveness on related imaging features (average $r = \pm 0.75$)
Wibmer et al.	Prolaris® test	MRI	ECE on MRI had significantly higher mean cell cycle risk score (reader 1: 3.9 vs. 3.2, $p = 0.015$; reader 2: 3.6 vs. 3.2, $p = 0.045$)
Vander-Weele et al.	PTEN	mpMRI	Imaging uptake parameters showing mathematical correlation with PTEN expression ($r = 0.25$, $p < 0.1$ and $r = 0.43$, $p < 0.01$), and T2w unevenness also showed some correlation tendency ($r = -0.25$, $p < 0.1$)
Switlyk et al.	PTEN	MRI	ADC was negatively correlated with Gleason score ($p = 0.001$) and tumor size ($p = 0.023$)

Larger prospective, multicenter studies and protocol to standardize imaging features

Identification and validation of relevant imaging biomarkers

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Closing remarks

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The need for well-designed clinical trials … …

- **Better dose distribution, higher LET and RBE are expected to be powerful in clinical setting**
- **Direct evidence of superiority is not still confirmed**
- **Cost-effectiveness remains a challenge**
- **Patient's preferences is an obstacle to conduct large scale randomized clinical trials**
- **OS, DFS, and bRFS are not probably the more suitable endpoints**
- **Radiomics, Dosiomics, and Radiogenomics should be incorporate into decision-making process**
- **Other specific biomarkers/biosignatures for radiosensitivity need to be validate**
- **A special issue is immunotherapy, with a possible role of increased immunogenicity**
- **Integration of imaging, dosimetry, and molecular data can realize the "Precision Radiation"**

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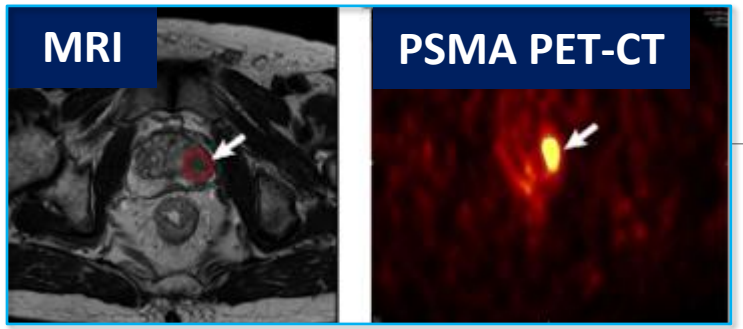
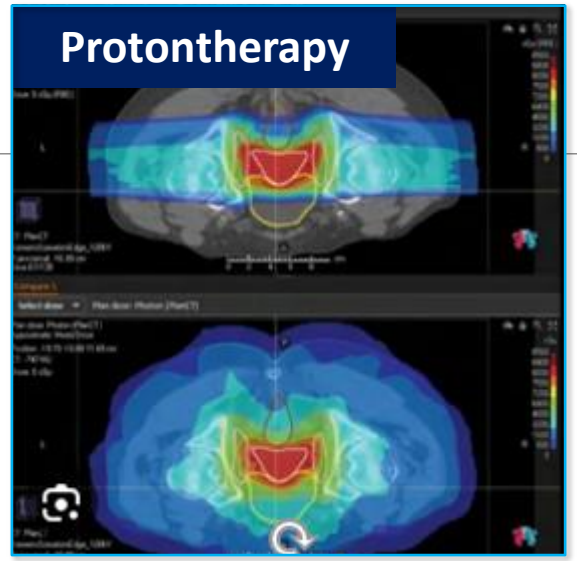
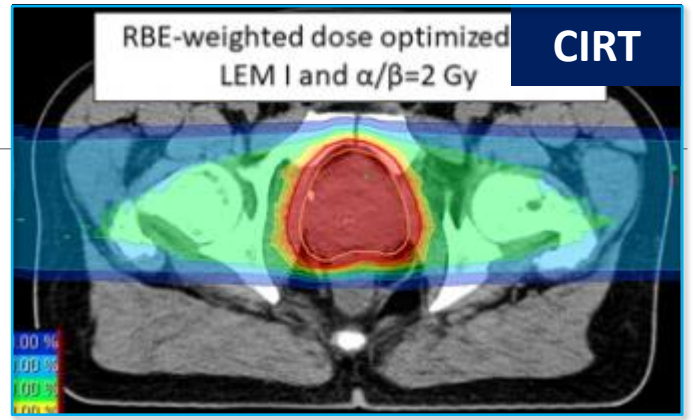
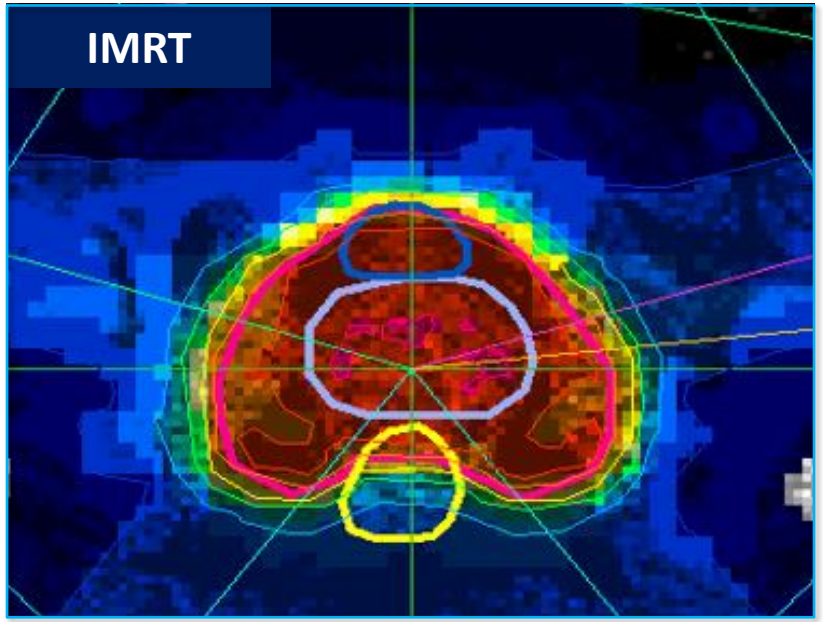
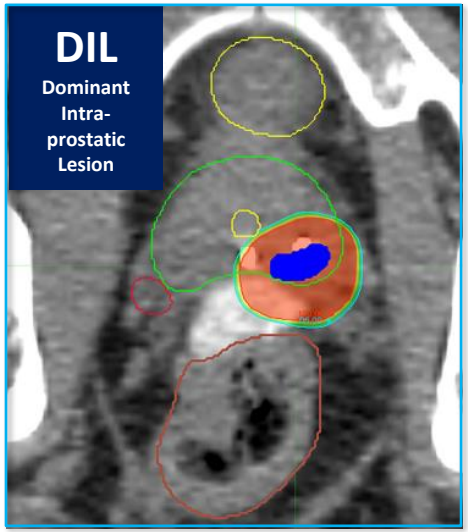
The challenge: Precision and Personalized Treatment

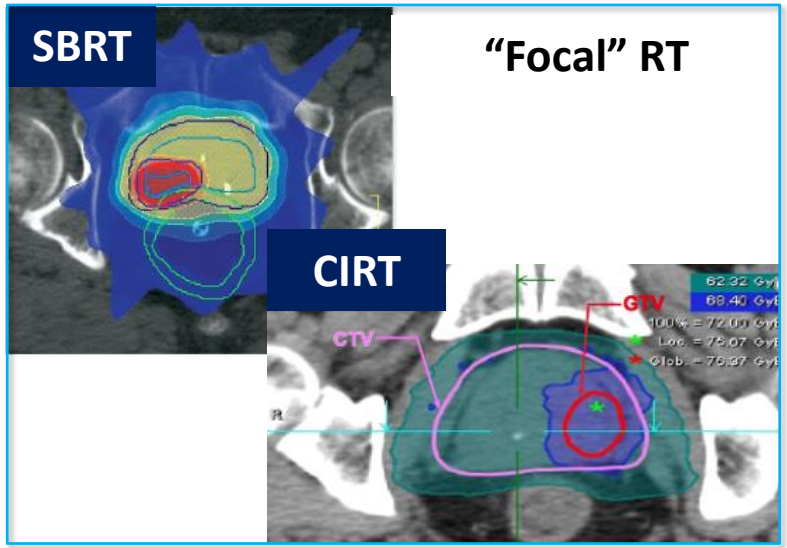












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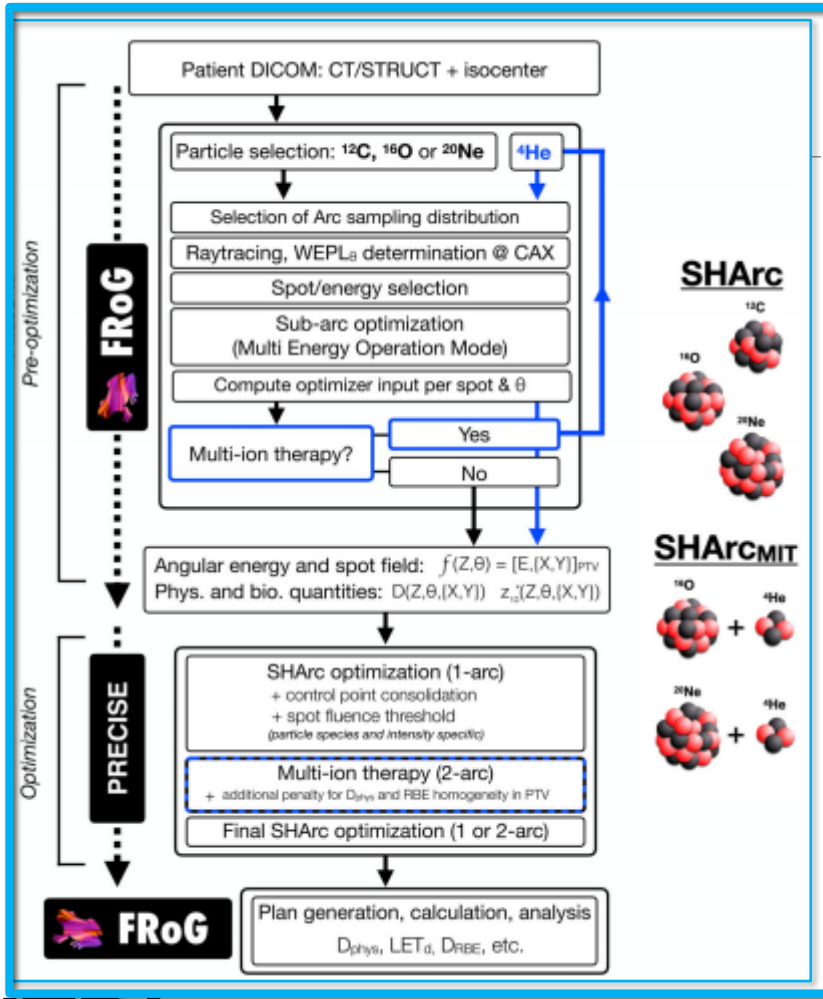
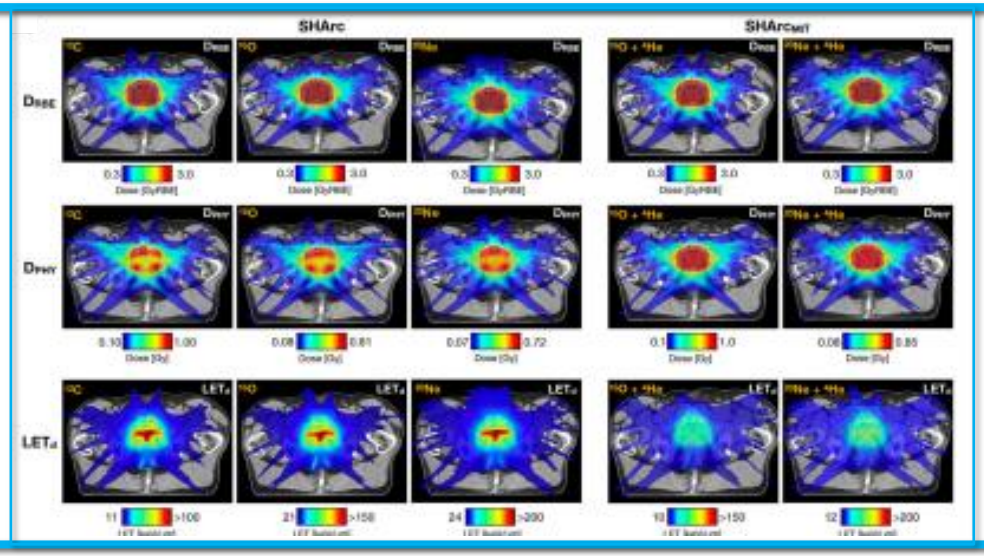
Multi-ion therapy and dynamic delivery



Spot-scanning hadron arc (SHArc) therapy: A proof of concept using single- and multi-ion strategies with helium, carbon, oxygen, and neon ions

Biologically robust treatment is feasible combining heavy and light ions in a single arc-field, yielding uniform and unique effective dose within the CTV, and homogeneous distributions of RBE

Multi-Ions (Proton, helium, carbon, oxygen, and/or neon) can improve target conformality and reduce dose and LET in normal tissue



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Thank You !!!

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